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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/692,299

10/22/2003

Napoleone Ferrara

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EXAMINER

HUYNH, PHUONG N

ART UNIT

PAPER NUMBER

1644

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

01/05/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/692,299

Applicant(s)

FERRARA ET AL.

Examiner

Phuong Huynh

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 6-25 is/are pending in the application.
- 4a) Of the above claim(s) 13-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 6-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 January 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>10/6/06</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Sequence alignment</u> . |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/6/06 has been entered.
2. Claims 1 and 6-25 are pending.
3. Claims 13-25 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.
4. Claims 1 and 6-12, drawn to EG-VEGF polypeptide, are being acted upon in this Office Action.
5. The disclosure is objected to because of the following informalities: (1) "Figures 20A-P" in The Brief Description of Drawing at page 12, line 10 should have been "Figures 20A-Q". (2) "Figure 19" at page 11, line 21 should have been "Figure 19A-N" to correspond to the drawing.
6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.
7. The information disclosure statement, filed 10/6/06, has been considered. The BLAST results demonstrate that applicants are aware of nucleic acid and polypeptide sequences with identity to the one claimed herein. However, as the BLAST results do not give sufficient identifying information, the Examiner cannot determine if said sequences constitute prior art.
8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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9. Claims 1, 6-10 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated human EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (2) an isolated mature human EG-VEGF polypeptide comprising amino acid residues 20 to 105 of SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (3) the isolated EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells is a human endocrine gland-derived vascular endothelial growth factor (EG-VEGF) and useful for screening assays, (4) An isolated EG-VEGF polypeptide comprising the amino acid residues 20 to 105 of SEQ ID NO: 2 or the polypeptide of SEQ ID NO: 2 fused to a heterologous polypeptide selected from the group consisting of an Fc and His-tag wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, **does not** reasonably provide enablement for (1) any isolated EG-VEGF polypeptide "having at least 95% amino acid sequence identity" with the amino acid sequence of residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (2) any isolated polypeptide comprising any "amino acid sequence" comprising amino acid residues 20 to 105 of SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (3) any isolated EG-VEGF polypeptide comprises "at least 95% amino acid sequence identity" to SEQ ID NO: 2, wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (4) any isolated polypeptide comprising "an amino acid sequence" comprising SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (5) any isolated EG-VEGF polypeptide "having at least 95% amino acid sequence identity" with the amino acid sequence of residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide is a "native sequence" of any endothelial gland-derived vascular endothelial growth factor (EG-VEGF), (6) any isolated EG-VEGF polypeptide "having at least 95% amino acid sequence identity" with the amino acid sequence of residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide is any "allelic variant" of any EG-VEGF, (7) any isolated EG-VEGF polypeptide "having at least 95% amino acid sequence identity" with the amino acid sequence of residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide is a human native sequence of endothelial gland-derived vascular endothelial growth factor (EG-VEGF) and promotes proliferation of adrenal cortex-derived capillary endothelial cells for treating any

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diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 1 and 7 encompass any isolated EG-VEGF polypeptide having at least about 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2 or comprising at least 95% identity to SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells.

Claims 6 and 8 encompass any isolated EG-VEGF polypeptide comprising any "amino acid sequence" comprising amino acid residues 20 to 105 of SEQ ID NO: 2 or SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells.

Claims 9, 10 and 11 encompass any native sequence and any allelic variant of any EG-VEGF polypeptide having at least about 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2.

The specification discloses only one isolated human EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, see page 10, Figure 13A. The secreted or mature EG-VEGF polypeptide comprises amino acid residues 20 to 105 of SEQ ID NO: 2. The specification also discloses the mature EG-VEGF polypeptide comprising residues 20 to 105 of SEQ ID NO: 2 fused to Fc of immunoglobulin or His Tag wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, see page 99, Example 14. The specification theorizes the isolated EG-VEGF polypeptide is useful for drug screening (page 54-56), production of antibody that binds specifically to EG-VEGF (See page 65) and *may be* useful for treating disease. The mature protein is from residues 20 to 105 of SEQ ID NO: 2. The

specification further discloses that EG-VEGF is expressed in the endocrine tissues such as the stroma cell and granulosa cells in the ovary, the Leydig cell in the testis, the adrenal gland and the placenta. The EG-VEGF is mitogenic and chemo attractant for specific endothelial cells but not human aortic vascular smooth muscle cells, pericytes, fibroblast, human neonatal fibroblasts and keratinocytes. The angiogenic effect of EG-VEGF is tissue specific since EG-VEGF has no effect on rat corneal pocket assay. The specification further discloses that injection of Adenoviral vector carrying the human EG-VEGF cDNA or VEGF causes an increase in angiogenesis, large fluid-filled or hemorrhagic cystic formation in ovary (Fig. 19).

The term "native sequence EG-VEGF" as defined in the specification at page 12-13 encompasses any "naturally-occurring truncated or secreted forms (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally occurring allelic variants of the EG-VEGF". The term "EG-VEGF variant polypeptide" as defined in the specification at page 13, lines 16 "includes, for instant, EG-VEGF polypeptide wherein one or more amino acid residues are added, or deleted, at the N- and/or C-terminus as well as within one or more internal domains, of the sequence of Figure 2 (SEQ ID NO: 2)".

However, the specification does not teach how to make any EG-VEGF polypeptide mentioned above without guidance as to which amino acids within the full-length sequence of SEQ ID NO: 2 to be modified by substitution, deletion, addition or combination thereof such that the modified EG-VEGF having at least 95% amino acid sequence identity with the residues 20 to 105 of SEQ ID NO: 2 or having at least 95% sequence identity to SEQ ID NO: 2 maintains its structure and function. The specification does not teach how to make any naturally-occurring truncated or secreted forms (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally occurring allelic variants of EG-VEGF that have at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2 or SEQ ID NO: 2. An isolated polypeptide without the amino acid sequence has no structure, much less function. The specification has not identified which amino acids within the one or more internal domains of the full-length sequence of SEQ ID NO: 2 or the mature sequence from residues 20 to 105 of SEQ ID NO: 2 can be substituted, deleted, added or combination thereof such that the resulting modified EG-VEGF polypeptide still maintains its three dimensional structure and function to promote proliferation of adrenal cortex-derived capillary endothelial cells (ACE). The specification has not identified which amino acids within SEQ ID NO: 2 that are essential for the desired biological activity such as promoting proliferation

of adrenal cortex-derived capillary endothelial cells. Other than the human EG-VEGF comprising the amino acid sequence of SEQ ID NO: 2 and the mature EG-VEGF polypeptide comprising the residues 20-105 of SEQ ID NO: 2, the specification as filed does not teach the structure of any naturally-occurring variant such as alternatively spliced forms or allelic variant of any EG-VEGF polypeptide mentioned above. Further, the term “having” or “comprising” is open-ended. It expands the residues 20 to 105 to include additional amino acids at either or both ends. There is insufficient guidance as to which amino acids to be added. It is known in the art that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. Without the amino acid sequence, one of skill in the art cannot make, much less use the claimed polypeptide.

It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al, of record, in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495; PTO 1449). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Attwood et al, of record, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document).

Skolnick et al, of record, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Bullock et al (Mol Pharmacol 65: 582-588, 2004; PTO 892) teach prokineticins (PKs) are newly identified secreted cysteine rich proteins that possess diverse biological functions, including gastrointestinal motility, angiogenesis, and circadian rhythms (see page 582, col. 1, in particular). The reference human prokineticin 1 (PK1) is 100% identical to the claimed human EG-VEGF that promotes angiogenesis particularly in a number of endocrine organs as referenced to LeCouter et al references 2001, 2003 therein (see page 582, col. 1, in particular) and the BLAST results in PTO1449 filed 10/6/06. Bullock et al teach adding or substituting one amino acid at the N-terminus of prokineticin 1 such as A1MPK1, MetPK1 and Ala6PK1 resulted in mutated

prokineticins that were completely devoid of biological activities (see page 586, Table 1, page 584, col. 1, first paragraph, in particular). Bullock et al teach substituting alanine 1 of PK1 with methionine (A1MPK1) or adding a methionine to the N-terminal of PK1 resulted in loss of activation of PK1 through the prokineticins receptor, and resulted in loss of prokineticin promoted proliferation of cells expressing the prokineticin receptor (see entire document, page 584, col. 1, second paragraph, in particular). Bullock et al conclude that both N- and C-terminal domains of prokineticins contribute to their bioactivities and neither domain is efficient for receptor activation (see page 587, col. 1, in particular).

Negri et al (British J of Pharmacology 146: 625-632, 2005; PTO 892) teach a small protein Bv8, isolated from the skin of the closely related frogs *Bombina variegata* and *B. bombina* which belongs to the family of secreted proteins of about 80 amino acids in the venom of the black mamba *Dendroaspis polylepis*, in rodents (mouse: mBv8 or prokineticin 2 (PK2); rat prokineticins, and humans (EG-VEGF or prokineticin 1 (PK1) (see page 625, col. 1, in particular). All these proteins have the same amino terminal sequence AVITAG (see page 625, col. 1, in particular). Negri et al further teach deletion of the first two amino acids of Bv8 still bind to prokineticin receptors, but their ability to activate them is changed, resulting in abolished any biological activity, both in vitro and in vivo (see entire document, page 630, col. 1, in particular).

Given the unlimited number of EG-VEGF polypeptide, allelic variant and native sequence having merely 95% sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO: 2, or at least 95% identity to SEQ ID NO: 2, there is insufficient in vivo working example showing any undisclosed EG-VEGF variant and any native sequence that "includes EG-VEGF polypeptide wherein one or more amino acid residues are added, or deleted, at the N- and/or C-terminus as well as within one or more internal domains, of the sequence of Figure 2 (SEQ ID NO: 2)" promotes proliferation of adrenal cortex-derived capillary endothelial cells. As such, the specification merely extends an invitation to one of skilled in the art to come up with the structure to arrive at the claimed invention. Although the specification describes how to screen EG-VEGF polypeptides for ACE cell proliferation activity, screening or identification of activity once the EG-VEGF polypeptide has been made, does not cure the lack of teaching regarding how to make the variants to be test for activity. Without such guidance, the changes which can be made in the EG-VEGF polypeptide comprising SEQ ID NO: 2 or the amino acid residues 20 to 105 of SEQ ID NO: 2 and still maintain its activity is unpredictable. Accordingly,

an undue amount of experimentation would be required to determine how to practice the claimed invention.

With regard to “allelic variant” of EG-VEGF, the specification does not provide any particular definition for the term allele. The specification discloses only one human EG-VEGF within the genus of EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2. There is no guidance as how the structure of SEQ ID NO: 2 related to the structure of any other allelic variant. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele EG-VEGF is representative of unknown alleles. The nature of allelic variant is that they are variant structures, and in the present state of the art the structure does not provide guidance to the structure of the others.

Further, the specification does not provide guidance of alternative spliced or naturally occurring forms of EG-VEGF polypeptides. The specification does not provide any structure, e.g. sequence that distinctly identifies all the known and unknown alternatively spliced variants of any EG-VEGF. There is no working examples for making any allelic variant of EG-VEGF, the corresponding nucleic acid encoding any naturally occurring allelic variant of EG-VEGF comprising SEQ ID NO: 2 or the amino acid sequence residues 20 to 105 of SEQ ID NO: 2.

Carmeliet et al (Nature 412: 868-869, August 2001; PTO 892) teach “EG-VEGF and VEGF are structurally dissimilar and probably work through different receptors” (see page 868, col. 3, second full paragraph, in particular). VEGF affects endothelial cells non-selectively, and even acts on non-endothelial cells such as motor neurons. EG-VEGF on the other hand, affects only endothelial cells in endocrine glands. Without such guidance as to the structure of any allelic variant and still maintain its activity is unpredictable. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With respect to “comprising *an amino acid sequence* comprising amino acid residues 20 to 105 of SEQ ID NO: 2” in claim 6 and “comprising *an amino acid sequence* comprising SEQ ID NO: 2” in claim 8, there is insufficient guidance as to the structure without the amino acid sequence of any such isolated polypeptide recited in claims 6 and 8.

The specification discloses the mature EG-VEGF polypeptide comprising residues 20 to 105 of SEQ ID NO: 2 fused to immunoglobulin Fc or His Tag wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, see page 99, Example 14. Other than the heterologous polypeptide selected from the group consisting of Fc and His tag fused to SEQ ID NO: 2 or the mature polypeptide from residues 20 to 105 of SEQ ID NO: 2, the

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specification does not teach the structure, such as the "amino acid sequence" to be added at either or both ends of amino acid residues 20 to 105 of SEQ ID NO: 2 or the polypeptide of SEQ ID NO: 2 wherein the polypeptide still promotes proliferation of adrenal cortex-derived capillary endothelial cells in vitro or in vivo.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In *re wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 10/6/06 have been fully considered but are not found persuasive.

Applicants' position is that claim 1 has been amended to encompass an isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO: 2. The language of the claim, which is consistent with the description in the specification (e.g., at page 13, line 30 to page 14, line 3), specifies that the claimed polypeptide contains the amino acid sequence of mature EG-VEGF (residues 20-105 of SEQ ID NO: 2 or a sequence having at least 95% identity to residues 20-105). The claims also require that the isolated polypeptide promotes proliferation of ACE endothelial cells. The definition of "EG-VEGF variant polypeptide" is clearly described in the specification. On page 13 and 14, "EG-VEGF variant polypeptide" is defined as an active EG-VEGF polypeptide having at least about 95% amino acid sequence identity with the amino acid sequence of (a) residues 1 or about 20 to 105 of SEQ ID NO: 2, (b) X to 105 of SEQ ID NO: 2 wherein X is any amino acid residue from 14 or 24 of SEQ ID NO: 2, or (c) another specifically derived fragment of the amino acid sequence of SEQ ID NO: 2. As such, one of ordinary skill in the art reading this definition would understand that EG-VEGF variant polypeptides as described in the application fall into three different, albeit related categories. Comparing this definition to the presently amended claim 1, it is apparent that the presently amended claim 1 is directed to a part of category (a) under this definition (EG-VEGF variants having at least 95% amino acid sequence identity with the amino

acid sequence of residues 20-105 of SEQ ID NO: 2). In contrast, the Examiner's reading of claim 1 appears to rely on category (b) or (c) of the definition. Citing Ngo et al., Attwood et al., and Skolnick et al., the Office Action alleges the relationship between an amino acid sequence and its activity is unpredictable and that current sequence based methods for predicting structure and function are inadequate and unreliable. Brenner et al., however, discloses that % sequence identity comparison methods are adequate and useful for predicting shared function (Brenner et al., 1998, Science, 95:6073-6078). In addition, angiogenic factors, such as VEGF, were known to exist in families having high amino acid sequence identity. See, for example, Tables 1 and 2 in the prior response. As discussed in the prior response, the post filing publications of LeCouter et al., Masuda et al., and Bilious et al. confirm that SEQ ID NO: 2 is a member of a family having high amino acid sequence identity. Mature mouse, rat, and bovine EG-VEGF have at least 88% amino acid sequence identity with mature human EG-VEGF (residues 20-105 of SEQ ID NO: 2). See Table 1 in the prior response. Therefore, one of skill in the art would have reasonably expected EG-VEGF, an angiogenic factor, to be a member of a protein family (including variants and homologs) having high amino acid sequence identity. On page 7 of the remarks filed 10/6/06, applicants argue that the specification teaches different ways to determine whether an isolated EG-VEGF polypeptide sharing high percentage of sequence identity to the full length or mature form of the native EG-VEGF (SEQ ID NO: 2) is capable of promoting proliferation of adrenal cortex-derived capillary endothelial cells. For example, Example 14 describes how to screen EG-VEGF polypeptides for ACE cell proliferation activity.

In response, it is acknowledged that the amended claims provide functional limitation that isolated EG-VEGF polypeptide promotes proliferation of adrenal cortex-derived endothelial cells. However, The nature and breadth of claims 1 and 7 encompass any isolated EG-VEGF polypeptide having at least about 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2 or comprising at least 95% identity to SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells. Claims 6 and 8 encompass any isolated EG-VEGF polypeptide comprising any "amino acid sequence" comprising amino acid residues 20 to 105 of SEQ ID NO: 2 or SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells. Claims 9, 10 and 11 encompass any native sequence and any allelic variant of any EG-VEGF polypeptide having at least about 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2.

The specification discloses only one human EG-VEGF within the genus of human EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or amino acid residues 20 to 105 of SEQ ID NO: 2. The specification does not teach how to make and use any EG-VEGF polypeptide mentioned above that encompassed any naturally-occurring truncated or secreted forms (e.g., an extracellular domain sequence), any naturally-occurring variant forms (e.g., alternatively spliced forms) and any naturally occurring allelic variants of the EG-VEGF without the amino acid sequence. An isolated polypeptide without the amino acid sequence has no structure, much less function. The specification has not identified which amino acids within the one or more internal domains of the full-length sequence of SEQ ID NO: 2 or the mature sequence from residues 20 to 105 of SEQ ID NO: 2 can be substituted, deleted, added or combination thereof such that the resulting modified EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO: 2 or having at least 95% identity to SEQ ID NO: 2 still maintains its three dimensional structure and function to promote proliferation of adrenal cortex-derived capillary endothelial cells (ACE). The specification has not identified which amino acids that are essential for the desired biological activity such as promoting proliferation of adrenal cortex-derived capillary endothelial cells. Without such guidance, the changes which can be made in the EG-VEGF polypeptide comprising SEQ ID NO: 2 or the amino acid residues 20 to 105 of SEQ ID NO: 2 and still maintain its activity is unpredictable. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With respect to the Brenner et al reference, Brenner et al neither teach sequence identity comparison for the claimed EG-VEGF, nor the function of EG-VEGF.

Attwood et al, of record, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document).

Skolnick et al, of record, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Further, Bullock et al (Mol Pharmacol 65: 582-588, 2004; PTO 892) teach that adding or substituting even one amino acid at the N-terminus of prokineticin 1, which has amino acid sequence 100% identical to the claimed human EG-VEGF polypeptide, such as A1MPK1,

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MetPK1 and Ala6PK1 resulted in mutated prokineticins that were completely devoid of biological activities (see page 586, Table 1, page 584, col. 1, first paragraph, in particular).

Negri et al (British J of Pharmacology 146: 625-632, 2005; PTO 892) teach a small protein Bv8, isolated from the skin of the closely related frogs *Bombina variegata* and *B. bombina* which belongs to the family of secreted proteins of about 80 amino acids in the venom of the black mamba *Dendroaspis polylepis*, in rodents (mouse: mBv8 or prokineticin 2 (PK2); rat prokineticins, and humans (EG-VEGF or prokineticin 1 (PK1) (see page 625, col. 1, in particular). All these proteins have the same amino terminal sequence AVITAG (see page 625, col. 1, in particular). Negri et al further teach deletion of the first two amino acids of Bv8 still bind to prokineticin receptors, but their ability to activate them is changed, resulting in abolished any biological activity, both in vitro and in vivo (see entire document, page 630, col. 1, in particular).

Contrary to applicant's assertion that EG-VEGF and VEGF were known to exist in families having high amino acid sequence identity, Carmeliet et al (Nature 412: 868-869, August 2001; PTO 892) teach "EG-VEGF and VEGF are **structurally dissimilar** and probably work through different receptors" (see page 868, col. 3, second full paragraph, in particular). In fact, Bullock et al teach prokinecticin-1 (EG-VEGF) binds through the prokineticins receptor, and resulted in loss of prokineticin promoted proliferation of cells expressing the prokineticin receptor (see entire document, page 584, col. 1, second paragraph, in particular). Further, Carmeliet et al teach VEGF affects endothelial cells non-selectively, and even acts on non-endothelial cells such as motor neurons. EG-VEGF on the other hand, affects only endothelial cells in endocrine glands.

The specification discloses only one allele within the genus of human EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or the mature human EG-VEGF comprising amino acid residues 20 to 105 of SEQ ID NO: 2. There is no guidance as how the structure of SEQ ID NO: 2 related to the structure of any other allelic variants of any EG-VEGF. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele EG-VEGF is representative of unknown alleles. The nature of allelic variant is that they are variant structures, and in the present state of the art the structure does not provide guidance to the structure of the others. The specification does not provide any structure, e.g. sequence that distinctly identifies all the known and unknown alternatively spliced variants of EG-VEGF. There are no working examples for making any allelic variant of EG-

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VEGF, or the corresponding nucleic acid encoding any naturally occurring allelic variant of EG-VEGF comprising SEQ ID NO: 2 or the amino acid sequence residues 20 to 105 of SEQ ID NO: 2. Without such guidance as to the structure of any allelic variant and still maintain its activity is unpredictable. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With respect to the argument that the specification provides guidance how to screening for proliferation of adrenal cortex-derived capillary endothelial cells, screening or identification of activity once the EG-VEGF polypeptide has been made, does not cure the lack of teaching regarding how to make the variants to be test for activity.

10. Claims 1, 6-10 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any isolated EG-VEGF polypeptide “having at least 95% identity” to amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (2) any isolated EG-VEGF polypeptide comprising “at least 95% identity” to SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (3) any isolated polypeptide comprising any “amino acid sequence comprises” amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (4) any isolated EG-VEGF comprising “an” amino acid sequence of SEQ ID NO: 2, wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (5) any “native sequence” and (6) any “allelic variant” of any EG-VEGF polypeptide “having at least 95% amino acid sequence identity with the amino acid of residues 20 to 105 of SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells.

Claims 1 and 7 encompass any isolated EG-VEGF polypeptide having at least about 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2 or comprising at least 95% identity to SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells.

Claims 6 and 8 encompass any isolated EG-VEGF polypeptide comprising any “amino acid sequence” comprising amino acid residues 20 to 105 of SEQ ID NO: 2 or SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells.

Claims 9, 10 and 11 encompass any native sequence and any allelic variant of any EG-VEGF polypeptide having at least about 95% identity to amino acid residues 20 to 105 of SEQ ID NO: 2.

The specification discloses only *one* isolated human EG-VEGF polypeptide comprising *the* amino acid sequence of SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, see page 10, Figure 13A. The secreted or mature EG-VEGF polypeptide comprises amino acid residues 20 to 105 of SEQ ID NO: 2. The term “native sequence EG-VEGF” as defined in the specification at page 12-13 encompasses any “naturally-occurring truncated or secreted forms (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally occurring allelic variants of the EG-VEGF”. The term “EG-VEGF variant polypeptide” as defined in the specification at page 13, lines 16 “includes, for instant, EG-VEGF polypeptide wherein one or more amino acid residues are added, or deleted, at the N- and/or C-terminus as well as within one or more internal domains, of the sequence of Figure 2 (SEQ ID NO: 2)”.

The specification has not adequately described which amino acids within the full-length sequence of SEQ ID NO: 2 or the amino acid residues 20 to 105 of SEQ ID NO: 2 to be substituted, deleted, added and/or combination thereof such that the EG-VEGF variant maintains its structure and still promotes proliferation of adrenal cortex-derived capillary endothelial cells. The term “having” or comprising” is open ended. It expands the amino acid residues 20 to 105 of SEQ ID NO: 2 to include additional amino acids at either or both ends. Further, the specification does not provide any particular definition for the term allelic variant. The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutational sites, see Rieger et al, Glossary of Genetics (1991, page 16, in particular). The specification discloses only one allelic variant within the genus of human EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or the amino acid residues 20 to 105 of SEQ ID NO: 2. There is no disclosure as how the structure of SEQ ID NO: 2 or the mature protein comprising amino acid residues 20 to 105 of SEQ ID NO: 2 related to the structure of any

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other allelic variant of any EG-VEGF, any EG-VEGF such as human EG-VEGF. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele EG-VEGF is representative of unknown alleles. The nature of allelic variant is that they are variant structures, and in the present state of the art the structure does not provide guidance to the structure of the others. The common attributes of the genus of EG-VEGF are not described. There is not a single allelic variant or native sequence comprising an amino acid sequence having at least 95% sequence identity with the amino acid sequence comprising SEQ ID NO: 2 or having at least 95% sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO: 2. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is sufficient to support the claim.

Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 10/6/06 have been fully considered but are not found persuasive.

Applicants' position is that claim 1 has been amended to encompass an isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO: 2. The language of the claim, which is consistent with the description in the specification (e.g., at page 13, line 30 to page 14, line 3), specifies that the claimed polypeptide contains the amino acid sequence of mature EG-VEGF (residues 20-105 of SEQ ID NO: 2 or a sequence having at least 95% identity to residues 20-105). The claims also require that the isolated polypeptide promotes proliferation of ACE endothelial cells. The definition of "EG-VEGF variant polypeptide" is clearly described in the specification. On page 13 and 14, "EG-VEGF variant polypeptide" is defined as an active EG-VEGF polypeptide having at least about 95% amino acid sequence identity with the amino acid sequence of (a) residues 1 or about 20 to 105 of SEQ ID NO: 2, (b) X to 105 of SEQ ID NO:2 wherein X is any amino acid residue from 14 or 24 of SEQ ID NO:2, or (c) another specifically derived fragment of the amino acid sequence of SEQ ID NO:2. As such, one of ordinary skill in the art reading this definition

would understand that EG-VEGF variant polypeptides as described in the application fall into three different, albeit related categories. Comparing this definition to the presently amended claim 1, it is apparent that the presently amended claim 1 is directed to a part of category (a) under this definition (EG-VEGF variants having at least 95% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO: 2). In contrast, the Examiner's reading of claim 1 appears to rely on category (b) or (c) of the definition. On page 45, the specification describes variants of EG-VEGF to include EG-VEGF derived from other species. Also described are nucleic acid probes derived from EG-VEGF useful to identify such variant species. As discussed in the prior response, non-human species of EG-VEGF having at least 80% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO: 2 were identified for murine, rat, and bovine species (see Table 1 of the prior response). As described in Example 14, EG-VEGF induced proliferation of ACE cells as did the angiogenic factor VEGF. Further, Example 20 demonstrates that like VEGF, EG-VEGF induced angiogenesis in ovarian tissue. As discussed in the prior response, angiogenic factors like VEGF were known to exist in protein families having high amino acid identity. Like VEGF and its variants, EG-VEGF is described in the specification, for example, at page 13 and 14 to include active EG-VEGF variants having at least 95% amino acid sequence identity with amino acid sequence of residues 20 to 105 of SEQ ID NO:2. As discussed above, active EG-VEGF variants having at least 88% amino acid sequence identity with the amino acid sequence of residues 20-105 of SEQ ID NO:2 were identified for murine, rat, and bovine species (see Table 1 of the prior response). Applicants also direct the Examiner's attention to Example 14 of the USPTO Revised Written Description Guidelines Training Materials. Example 14 outlines a written description analysis of a polypeptide claim that satisfies the requirement under 35 U.S.C. § 112, first paragraph. The claim in Example 14 is directed to a genus of polypeptides having at least 95% identity to a reference sequence (SEQ ID NO: 3) and a specific activity. The specification provided a novel and unobvious polypeptide sequence (SEQ ID NO:3) having a specific activity and an assay for identifying other proteins having the claimed specific activity. The specification did not disclose any variants of the polypeptide sequence. Applying the analysis set forth in Example 14 of the written description guidelines, Applicants submit the specification sufficiently describes the claimed genus of EG-VEGF polypeptides. Similar to the claim analyzed in Example 14, Applicants' claims are directed to a genus of EG-VEGF polypeptides that have 95% identity to mature EG-VEGF and promote proliferation of adrenal cortex-derived capillary endothelial cells.

Example 1 describes how to isolate cDNA clones encoding EG-VEGF, including the signal sequence finding computer algorithm used to identify the cDNA clones. Examples 2-6 teach expression of EG-VEGF. Example 14 describes an assay for detecting the cell proliferation activity of EG-VEGF. Specific nucleic acid sequences encoding EG-VEGF (nucleotides 91-405 of SEQ ID NO: 1 and SEQ ID NO:3) and amino acid sequence (SEQ ID NO:2) of EG-VEGF are taught in the specification. Methods for making EG-VEGF variants, including preferred amino acid substitutions are also disclosed. See, for example, page 31, line 24 to page 33, line 23.

In response, merely adding functional language to a sequence having at least 95% sequence identity to SEQ ID NO: 2 or residues 20 to 105 of SEQ ID NO: 2 without identifying which amino acids are critical for the function of the protein is not sufficient to overcome the written description requirement. The term "native sequence EG-VEGF" as defined in the specification at page 12-13 encompasses any "naturally-occurring truncated or secreted forms (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally occurring allelic variants of the EG-VEGF". The term "EG-VEGF variant polypeptide" as defined in the specification at page 13, lines 16 "includes, for instant, EG-VEGF polypeptide wherein one or more amino acid residues are added, or deleted, at the N- and/or C-terminus as well as within one or more internal domains, of the sequence of Figure 2 (SEQ ID NO: 2)".

However, the specification does not reasonably provide a **written description** of any "native sequence" or any "allelic variant" of any EG-VEGF polypeptide "having at least 95% amino acid sequence identity with the amino acid of residues 20 to 105 of SEQ ID NO: 2 or SEQ ID NO: 2, let alone any "allelic variant" of any EG-VEGF polypeptide "having at least 95% amino acid sequence identity with the amino acid of residues 20 to 105 of SEQ ID NO: 2 or SEQ ID NO: 2 promotes proliferation of adrenal cortex-derived capillary endothelial cells.

The specification discloses only *one* isolated human EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, see page 10, Figure 13A. The secreted or mature EG-VEGF polypeptide comprises amino acid residues 20 to 105 of SEQ ID NO: 2.

The specification does not provide any particular definition for the term allelic variant. The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutational sites, see Rieger et al, Glossary of Genetics

(1991, page 16, in particular). The specification discloses only one allelic variant within the genus of human EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or the mature or secreted polypeptide comprising amino acid residues 20 to 105 of SEQ ID NO: 2. There is no disclosure as how the structure of SEQ ID NO: 2 or the mature protein comprising amino acid residues 20 to 105 of SEQ ID NO: 2 related to the structure of any other allelic variant of any EG-VEGF, any EG-VEGF such as human EG-VEGF. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele EG-VEGF is representative of unknown alleles. The nature of allelic variant is that they are variant structures, and in the present state of the art the structure does not provide guidance to the structure of the others. The common attributes of the genus of EG-VEGF are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is sufficient to support the claim. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004):

With respect to the argument that the specification at page 45 describes variants of EG-VEGF to include EG-VEGF derived from other species, the specification at page 45 merely asserts the existence of other EG-VEGF variants to include EG-VEGF derived from other species. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116.). The specification as filed does not disclose any allelic variant sequences nor does it demonstrate that allelic variant of EG-VEGF polypeptides promotes proliferation of adrenal cortex-derived capillary endothelial cells. There is a lack of biochemical information such as amino acid sequence or nucleic acid sequence that distinctly identify variants of EG-VEGF that encompass any “naturally-occurring truncated or secreted forms (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally occurring allelic variants of the EG-VEGF to includes, for instant, EG-VEGF polypeptide wherein one or more amino acid residues are added, or deleted, at the N- and/or C-terminus as well as within one or more internal domains, of the sequence of Figure 2 (SEQ ID NO: 2)”.

Further, the specification has not adequately describe which amino acids with the full-length sequence of SEQ ID NO: 2 or the amino acid residues 20 to 105 of SEQ ID NO: 2 to be substitute, deleted, added and/or combination thereof such that the EG-VEGF variant maintains its structure and function. Further, the specification does not provide any particular definition for the term "allelic variant". The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutational sites, see Rieger et al, Glossary of Genetics (1991, page 16, in particular). The specification discloses only one allelic variant within the genus of human EG-VEGF polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or the amino acid residues 20 to 105 of SEQ ID NO: 2. There is no disclosure as how the structure of SEQ ID NO: 2 or the mature protein comprising amino acid residues 20 to 105 of SEQ ID NO: 2 related to the structure of any other allelic variant of any EG-VEGF, any EG-VEGF such as human EG-VEGF. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele EG-VEGF is representative of unknown alleles. The nature of allelic variant is that they are variant structures, and in the present state of the art the structure does not provide guidance to the structure of the others. The common attributes of the genus of EG-VEGF are not described. The specification discloses only one human EG-VEGF comprising the amino acid sequence of SEQ ID NO: 2, one of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is sufficient to support the claim. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

11. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "isolated EG-VEGF polypeptide having *at least 95%* amino acid sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO: 2 wherein the native sequence is an *allelic variant* of EG-VEGF" in claim 10 represents a departure from the specification and

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the claims as originally filed. The passages pointed out by applicant in the amendment filed 10/6/06 do not provide a clear support for the said phrase.

12. Priority given to some parent cases but not others:

According to the priority statement of October 22, 2003, Applicant claims priority to several U.S. non-provisional, PCT and U.S. provisional applications. Based on the information given by applicants and an inspection of the patent applications, the examiner has concluded that the subject matter defined in this application is supported by the disclosure in U.S. patent application serial number 09/886,242, filed June 20, 2001; which claimed benefit to provisional 60/230,978, filed September 7, 2000 but is not supported by any of the others for the following reasons. All the other applications disclose the DNA and amino acid sequence of PRO1186. However, only the 09/886,242 and 60/230,978 disclose an enabled use for PRO1186 or EG-VEGF polypeptide comprising SEQ ID NO: 2 or the mature polypeptide comprising residues 20 to 105 of SEQ ID NO: 2, namely, that it promotes proliferation of adrenal cortex-derived capillary endothelial cells. Accordingly, the subject matter in claims 6, 7, 8, 11 and 12 has an effective filing date of September 7, 2000. The filing date in claims 1, 9 and 10 is deemed to be the filing date of instant application, which is October 22, 2003. This is because none of the U.S. non-provisional, PCT and U.S. provisional applications have a written support and enablement for EG-VEGF having at least 95% amino acid sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO: 2 wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells" in claims 1, 9 and 10 as amended.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the US serial number, specific page and line numbers, sequence identifier of any parent applications filed prior to September 7, 2000 which specifically supports the claim limitation for each and every claim limitation in all the pending claims which applicant considers to have in possession *and* fully enabled of prior to September 7, 2000.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

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(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

14. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

15. Claims 1 and 6-12 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,485,938 B1 (filed November 14, 2000 and claimed benefit to provisional 60/165,905, filed Nov. 16, 1999; PTO 892).

The '938 patent teaches a native polypeptide such as the full-length human Zven2 comprising SEQ ID NO: 5 that has the amino acid sequence 100% identical to the claimed amino acid sequence of SEQ ID NO: 2, which is at least 95% amino acid sequence identity to the claimed SEQ ID NO: 2 (See SEQ ID NO: 5 of '938 patent, col. 51, line 13-14, in particular). The term "comprising" or "having" is open-ended. It expands the amino acid residues 20 to 105 of SEQ ID NO: 2 to include additional amino acids at either or both ends to include the reference polypeptide. Products of identical chemical composition (identical amino acid sequence) cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teach the identical chemical structure, the properties applicant discloses and/or claims such as promotes proliferation of adrenal cortex-derived capillary endothelial cells are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The reference human Zven inherently promotes adrenal cortex-derived capillary endothelial cells. Claim 10 is included in this rejection because the reference native sequence human Zven is one of the allele of the genus of EG-VEGF. Thus, the reference teachings anticipate the claimed invention.

16. The filing date of instant claims 1, 9 and 10 is deemed to be the filing date of instant application, which is October 22, 2003 as discussed above.

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17. Claims 1, 9 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by US Pat No 6,485,938 B1 (issued November 26, 2002, 1999; PTO 892).

The '938 patent teaches a native polypeptide such as the full-length human Zven2 comprising SEQ ID NO: 5 that has amino acid sequence 100% identical to the claimed amino acid sequence of SEQ ID NO: 2 (See SEQ ID NO: 5 of '938 patent, col. 51, line 13-14, enclosed sequence alignment, in particular). The term "comprising" or "having" is open-ended. It expands the amino acid residues 20 to 105 of SEQ ID NO: 2 to include additional amino acids at either or both ends to include the reference polypeptide. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teach the identical chemical structure, the properties applicant discloses and/or claims such as promotes proliferation of adrenal cortex-derived capillary endothelial cells are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The reference human Zven inherently promotes adrenal cortex-derived capillary endothelial cells. Thus, the reference teachings anticipate the claimed invention.

18. Claims 1 and 6-12 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 7,119,177 (filed November 15, 2001 which claimed priority to a provisional application 60/141,037 filed 6/23/1999; PTO 892).

The '177 patent teaches an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 371 (PRO1186), which is 100% identical to the claimed EG-VEGF polypeptide comprising SEQ ID NO: 2 of instant claim 11, and stimulates proliferation of adrenal cortical capillary endothelial (ACE) cells (see claim 1 of the '177 patent, reference SEQ ID NO: 371, see example 149, in particular). The claimed EG-VEGF polypeptide comprising SEQ ID NO: 2 and the reference polypeptide of SEQ ID NO: 371 comprises the same signal sequence (amino acid residues 1-19) and the mature polypeptide comprising residues 20 to 105 of SEQ ID NO: 2 lacking the signal peptide (see claim 1b of the '177 patent, in particular). The '177 patent also teaches various native human sequence and allelic variants of PRO1186 polypeptide, which includes an amino acid sequence comprising residues 20 through 105 of FIG. 266 (see, paragraph 2186, SEQ ID NO: 371 of the '177 patent) and various isolated polypeptides comprising an amino acid sequence having at least 95% sequence identity to the sequence of amino acid residues 20 to

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about 105, inclusive of FIG. 266 (SEQ ID NO: 371) (see paragraph 2187 of the '177 patent, in particular). Thus, the reference teachings anticipate the claimed invention.

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1 and 6-12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7,119,177. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

Claim 1 of instant application recites an isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells (genus). Claim 7 of instant application recites the isolated EG-VEGF polypeptide wherein the polypeptide comprises at least 95% identity to SEQ ID NO: 2 and wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells (genus). Claim 9 of

instant application recites the isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide is a native sequence. Claim 10 of instant application recites the isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide is an allelic variant of EG-VEGF. Claim 11 of instant application recites the isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the native sequence is SEQ ID NO: 2. Claim 12 of instant application recites the isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the native sequence is human.

Claim 1 of the '177 patent recites an isolated polypeptide comprising: (a) the amino acid sequence of the polypeptide of SEQ ID NO: 371; (b) the amino acid sequence of the polypeptide of SEQ ID NO: 371; lacking its associated signal peptide; (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203091. The polypeptide comprising SEQ ID NO: 371 is 100% identical to the EG-VEGF comprising SEQ ID NO: 2 and inherently promotes proliferation of adrenal cortex-derived capillary endothelial cells. The term "having" is open-ended. It expands the residues 20 to 105 of SEQ ID NO: 2 to include the signal peptide to include the polypeptide comprising SEQ ID NO: 371 of the '177 patent. The polypeptide comprising SEQ ID NO: 371 is a human native sequence. The polypeptide of SEQ ID NO: 371 lacking its associated signal peptide (claims 1(b) and 2 of the '177 patent) is the same polypeptide having 100% sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2 of instant application. Issuance of a patent to instant application (genus) would include the polypeptide of the '371 patent (species).

Claim 6 of instant application recites an isolated polypeptide comprising an amino acid sequence comprises amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide promotes the proliferation of adrenal cortex-derived capillary endothelial cells (genus). Claim 8 of instant application recites an isolated polypeptide comprising an amino acid sequence comprises SEQ ID NO: 2, wherein the polypeptide promotes the proliferation of adrenal cortex-derived capillary endothelial cells (genus).

Claim 3 of the '177 patent recites a chimeric polypeptide comprising a polypeptide according to claim 1 fused to a heterologous polypeptide. Claim 4 of the '177 patent recites the chimeric polypeptide of claim 3, wherein said heterologous polypeptide is an epitope tag or an Fc

region of an immunoglobulin (species). The issuance of a patent to a genus of claimed polypeptide would include the species of polypeptide and chimeric polypeptide of the issuance patent.

21. Claims 1 and 6-12 are directed to an invention not patentably distinct from claims 1-4 of commonly assigned U.S. Patent No. 7,119,177.

Specifically, claim 1 of instant application recites an isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells (genus). Claim 7 of instant application recites the isolated EG-VEGF polypeptide wherein the polypeptide comprises at least 95% identity to SEQ ID NO: 2 and wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells (genus). Claim 9 of instant application recites the isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide is a native sequence. Claim 10 of instant application recites the isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide is an allelic variant of EG-VEGF. Claim 11 of instant application recites the isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the native sequence is SEQ ID NO: 2. Claim 12 of instant application recites the isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the native sequence is human.

Claim 1 of the '177 patent recites an isolated polypeptide comprising: (a) the amino acid sequence of the polypeptide of SEQ ID NO: 371; (b) the amino acid sequence of the polypeptide of SEQ ID NO: 371; lacking its associated signal peptide; (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203091. The polypeptide comprising SEQ ID NO: 371 is 100% identical to the EG-VEGF comprising SEQ ID NO: 2 and inherently promotes proliferation of adrenal cortex-derived capillary endothelial cells. The term "having" is open-ended. It expands the residues 20 to 105 of SEQ ID NO: 2 to include the signal peptide to include the polypeptide comprising SEQ ID NO: 371 of the '177 patent. The polypeptide comprising SEQ ID NO: 371 is a human native sequence. The polypeptide of SEQ ID NO: 371 lacking its associated signal peptide (claims 1(b)

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and 2 of the '177 patent) is the same polypeptide having 100% sequence identity with the amino acid residues 20 to 105 of SEQ ID NO: 2 of instant application. Issuance of a patent to instant application would include the polypeptide of the '371 patent (species).

Claim 6 of instant application recites an isolated polypeptide comprising an amino acid sequence comprises amino acid residues 20 to 105 of SEQ ID NO: 2, wherein the polypeptide promotes the proliferation of adrenal cortex-derived capillary endothelial cells (genus). Claim 8 of instant application recites an isolated polypeptide comprising an amino acid sequence comprises SEQ ID NO: 2, wherein the polypeptide promotes the proliferation of adrenal cortex-derived capillary endothelial cells (genus).

Claim 3 of the '177 patent recites a chimeric polypeptide comprising a polypeptide according to claim 1 fused to a heterologous polypeptide. Claim 4 of the '177 patent recites the chimeric polypeptide of claim 3, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin (species). The issuance of a patent to a genus of claimed polypeptide would include the species of polypeptide and chimeric polypeptide of the issuance patent.

22. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 7,119,177, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

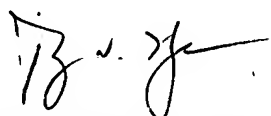
A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The

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examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

24. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Phuong N. Huynh, Ph.D.

Patent Examiner

December 22, 2006